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701-1

10:30

Local Arterial Wall Drug Delivery from a Polymer Coated Removable Metallic Stent: Kinetics, Distribution, and Bioactivity of Forskolin

*Neal L. Eigler, Thomas L. Lambert, Vishva Dev, Joel Kupfer, Ken Mahrer, James S. Forrester, *Frank Litvack, Cedars-Sinai Medical Center, Los Angeles, CA

We have developed a polyurethane coated removable metallic stent which incorporates milligram quantities of lipophilic drugs. Forskolin was chosen as the model drug because it is a small nonpolar molecule that can be incorporated into the coating and has antiplatelet and vasodilator properties. Our goal was to evaluate the kinetics, distribution, and bioactivity of local arterial delivery of forskolin. Stents ($n=15$) were deployed in the rabbit carotid for up to 24 hours. The quantity of forskolin bound to the stent decreased exponentially from 1580 ± 550 mg initially to 75 ± 6 mg at 24 hours (half-life of 5.8 hours). Blood concentrations peaked at 140 ± 39 pg/uL at 4 hours and remained elevated at 68 ± 18 pg/uL at 24 hours. The arterial flux of forskolin, initially 6.9 ± 1.9 ug/min decreased exponentially with a half-life of 1.2 hours. The adjacent arterial media contained 60 ± 39 ng/mg which was 380 and 460 times greater than the contralateral carotid media and the blood, respectively ($p < 0.0001$). Media forskolin concentrations declined over time with a tissue half-life of 5.0 hours. Drug distributed throughout the vessel wall with a decreasing gradient in the radial and axial dimensions, consistent with a diffusion process. Removal of the stent was associated with a 100-fold decline in media forskolin concentration within 2 hours. Forskolin release was associated with a sustained 74% increase in carotid flow and a 56% decrease in resistance ($p < 0.01$). In another set of rabbits ($n=14$) using a carotid crush injury, low flow model, forskolin prolonged the time to flow variation and occlusion by 12x compared to bare metal stents and 5x compared to polyurethane coated stents ($p < 0.0001$). Conclusions: A polymer coated stent can deliver forskolin to the arterial wall in high concentrations relative to the blood or other tissues. Local tissue and blood kinetics can be modeled as a simple diffusion process. Tissue forskolin levels are proportional to the drug remaining on the stent and are dependent on maintaining stent to tissue drug gradients. The delivered drug is biologically active demonstrating vasodilating and antiplatelet properties.

701-2

10:45

Local Delivery of Heparin with a PTCA Infusion Balloon Inhibits Platelet-dependent Thrombosis

Clifford N. Thomas,*James J. Barry, Spencer B. King III, Neal A. Scott. Division of Cardiology, Emory University Medical School, Atlanta, GA

Thrombosis is a major component of acute coronary syndromes and is associated with acute closure during PTCA. To assess the feasibility of local heparin delivery during PTCA, we compared the efficacy of systemic heparin administration and local delivery of heparin using a specially-designed PTCA balloon catheter with intramural channels for site-specific drug delivery. Thrombogenic Dacron graft segments were inserted into chronic arteriovenous shunts in pigs. Autologous platelets were labeled with $^{111}\text{Indium}$. Platelet deposition was quantitated with gamma camera imaging over a two hour period. The Dacron graft was exposed to flowing blood for 15 minutes in order to allow for mural thrombus formation. The infusion balloon was then deployed at the site of the thrombus, and heparin was infused over a five minute period. The balloon was then deflated and removed, and flow was re-established.

Platelet Deposition ($\times 10^{-8}$)

701-4

Transfer of Microparticles to Arteries Using the Microinfusion Catheter

Keith A. Robinson, Ron C. Gustavo D. Cipolla,*Stev Spencer B. King III, Emory

Attempts to inhibit formalin-induced thrombosis in animal models, using locally modified balloon catheter, sustained release of simple drug carriers has potential. We investigated the capacity of (Corporation) to transfer 30 nm gold particles to the sites of balloon injury (LCX) and LCX) were injured at 1 atm driving pressure, then fixed with glutaraldehyde after 10 min. After infusion with si

Deposition of gold microparticles with uniform circumferential thick sections by light microscopy. Gold microparticles were found to be retained within the endothelial lining of the injured artery.

Previous work by our group demonstrated that intracoronary thrombolytic delivery using conventional PTCA. The deposition following local urokinase delivery was measured by dilution with urokinase solution for 1 minute (at 4 atm for 5 minutes) by intravascular ultrasound. The same-size uncoated balloons were surgically removed and counted.

RESULTS: In 10 out of 12 animals, the mean decrease in platelet deposition in the treated vessels was 1.34 ± 1.6 .

CONCLUSION: Local infusion of urokinase-treated balloons reduces platelet deposition and may decrease intravascular angioplasty.

990-3

A Windows Software Application to Assess Arterial Dynamic Behavior: a Useful Tool in Laboratory and Non invasive Clinical Research.

*Marcelo R. Risk, Ricardo L. Armentano, Juan G. Barral, Carlos A. Perazzo, Ricardo H. Pichel, from the Teaching and Research Department, Favaloro Foundation, Buenos Aires, Argentina.

To fully characterize the cardiovascular system it is necessary to know in detail the dynamic behavior of the hydraulic load. The purpose of this work was to assess the parameters that characterize the arterial biodynamics obtained both from animal investigation (invasive) and patients (non invasive) studied in clinical centers of arterial hypertension. To this aim a software written in C++ for Windows enabling off line visualization and analysis of previously acquired signals was developed.

This software was designed to read ASCII file format to avoid incompatibility with the acquisition system, and it was divided into four blocks: 1) Identification, averaging and evaluation of hemodynamic signals of arterial pressure and diameter (beat to beat analysis) showing instantaneous temporal tracings and pressure-diameter loops, and calculation of purely elastic pressure-diameter relationship by elimination of the hysteresis loop enabling calculus of isobaric arterial compliance by means of three different theoretical models of the arterial wall. 2) Visualization of blood flow velocity obtained step by step at different depth into the arterial lumen, showing blood flow velocity profiles, the time variation of the velocity profile (obtained from a pulsed Doppler device) during the cardiac cycle, and the theoretical reconstruction of blood flow velocity assuming several models. 3) Calculation of arterial blood flow (from arterial diameter and cross sectional blood flow velocity) and analysis of arterial pressure and blood flow waveforms, showing beat to beat and averaged spectrum of arterial impedance. 4) Obtention and visualization of forward and backward waves of arterial pressure and flow from its original signals. In all cases printing output of graphics and data, as well as ASCII files of output data compatible with standard software, are enabled at any moment.

In conclusion, this software allows immediate analysis after basic and clinical research studies, independently of the signal sources, and taking into account elaborated mathematical models, therefore constituting a useful tool for the interpretation of the dynamic of the arterial behavior.

MONDAY AM

990-4

Automatic Accurate Analysis of Monophasic Action Potential Recordings

Michael R. Franz, C. Larissa Fabritz, Paulus F. Kirchhof, Bettina S. Koller, Madhus Zabel.

Divisions of Cardiology and Clin. Pharmacology, Georgetown University and VA Medical Center, Washington, DC.

Monophasic action potential (MAP) recordings are widely used in clinical and experimental studies but their manual measurement is cumbersome, especially when hundred or thousands of beats must be analyzed to monitor the exact time course of action potential duration (APD) changes. We developed a Macintosh-based computer program which automatically executes programmed electrical stimulation with up to 3 extrastimuli, stores 1 kHz MAP recordings to disk (up to 6 channels simultaneously), then analyzes APD at repolarization levels from 10 to 90% in 10% decrements and outputs numerical data automatically into spreadsheets or graphical displays. The algorithm "intelligently" reproduces the MAP analysis criteria developed in our laboratory: it identifies the fastest point on the upstroke phase, determines the maximum amplitude of the MAP plateau (unaffected by variations in "spike-and-dome" appearance or afterdepolarizations), returns the paced cycle length and calculates the electrical diastolic interval between MAPD-90% and the next upstroke. Validation was performed by comparing manual analysis by 2 independent observers (paper-speed 100 mm/sec) with computer generated data for a total of 608 MAP recordings. The table shows the results for APD at 3 repolarization levels as mean difference (milliseconds) \pm standard deviation.

	APD 20%	APD 50%	APD 90%
Computer minus observer 1	-2.0 \pm 8.8	-0.7 \pm 7.9	-0.2 \pm 8.5
Computer minus observer 2	-12.2 \pm 8.3	-5.8 \pm 7.5	-1.4 \pm 10.1
Observer 1 minus observer 2	-10.3 \pm 11.1	-5.1 \pm 9.0	-1.2 \pm 7.8

Paced cycle length vs. computer reported cycle length: error <0.2 \pm 0.7 msec.

Analysis of 100 MAP signals took approximately 2 hours by manual analysis and 1 min by computer. This program provides accurate, extremely efficient analysis of APD and cycle length.

701 Local Drug Delivery—Experimental Adjuncts to Angioplasty

Monday, March 14, 1994 10:30 AM-Noon
Georgia World Congress Center, Room 257W

701-1

10:30

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Platelet Deposition ($\times 10^{-8}$)

	45 min	60 min	100 min
Saline	5.0 ± 1.0	5.2 ± 1.1	5.8 ± 1.3
Heparin (500 U)	$1.4 \pm 0.4^*$	$1.9 \pm 0.9^*$	$1.6 \pm 1.0^*$
Heparin (5000 U)	$0.8 \pm 0.4^*$	$0.5 \pm 0.7^*$	$0.8 \pm 0.9^*$

* = $p < 0.05$

Local delivery of 500 U of heparin provided significantly more inhibition of platelet deposition than the 3000U systemic dose. We conclude that local delivery of heparin with a specially-designed infusion balloon catheter inhibits thrombosis at doses that are at least several fold less than the dose of heparin given systemically.

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PROGRAM AND
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